

# Age-dependent differences in the impact of paediatric traumatic brain injury on executive functions

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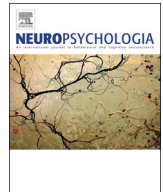
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# Age-dependent differences in the impact of paediatric traumatic brain injury on executive functions: A prospective study using susceptibility-weighted imaging

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## ABSTRACT

Childhood and adolescence represent sensitive developmental periods for brain networks implicated in a range of complex skills, including executive functions (EF; inhibitory control, working memory, and cognitive flexibility). As a consequence, these skills may be particularly vulnerable to injuries sustained during these sensitive developmental periods. The present study investigated 1) whether age at injury differentially affects EF 6 months and 2 years after TBI in children aged 5–15 years, and 2) whether the association between brain lesions and EF depend on age at injury. Children with TBI ( $n = 105$ ) were categorized into four age-at-injury groups based on previous studies and proposed timing of cerebral maturational spurts: early childhood (5–6 years,  $n = 14$ ), middle childhood (7–9 years,  $n = 24$ ), late childhood (10–12 years,  $n = 52$ ), and adolescence (13–15 years,  $n = 15$ ). EF were assessed with performance-based tasks and a parent-report of everyday EF. TBI patients' EF scores 6 months and 2 years post-injury were compared to those of typically developing (TD) controls ( $n = 42$ ). Brain lesions were identified using susceptibility weighted imaging (SWI). Results indicated that inhibitory control performance 2 years post-injury was differentially affected by the impact of TBI depending on age at injury. Follow-up analyses did not reveal significant differences within the age groups, preventing drawing strong conclusions regarding the contribution of age at injury to EF outcome after TBI. Tentatively, large effect sizes suggest that vulnerability is most apparent in early childhood and adolescence. Everyday inhibitory control behaviour was worse for children with TBI than TD children across childhood and adolescence at the 2-year assessment. There was no evidence for impairment in working memory or cognitive flexibility after TBI at the group level. Given small group sizes, findings from analyses into correlations between EF and SWI lesions should be interpreted with caution. Extent, number and volume of brain lesions correlated with adolescent everyday EF behaviour 6 months post-injury. Taken together, the results emphasize the need for long-term follow-up after paediatric TBI during sensitive developmental periods given negative outcomes 2-year post injury. Inhibitory

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control seems to be particularly vulnerable to the impact of TBI. Findings of associations between EF and SWI lesions need to be replicated with larger samples.

## 1. Introduction

Traumatic brain injury (TBI) is a common cause of childhood disability, affecting 691 per 100,000 children and adolescents per year across Western countries (Thurman, 2016). Paediatric TBI is associated with long-term cognitive impairments, with difficulties in the area of executive function (EF) being frequent and profound (Anderson and Catroppa, 2005; Babikian and Asarnow, 2009; Catroppa and Anderson, 2009; Mangeot et al., 2002; Sesma et al., 2008; van Heugten et al., 2006). EF are cognitive functions important for purposeful, goal-directed behaviour (Anderson, 2002; Diamond and Lee, 2011). They are essential for children's academic success and mental and physical health (Borella et al., 2010; Diamond, 2013; Gathercole et al., 2004). Their disruption can impact social participation and quality of life (Galvin et al., 2010; Levin et al., 2009, 1997; Rosema et al., 2012; Ylvisaker and Feeney, 2002). EF consist of three separable though interrelated constructs: inhibitory control, working memory and cognitive flexibility (Huizinga et al., 2006; Miyake et al., 2000). Inhibitory control refers to the ability to withhold dominant and pre-potent responses in contexts where they are not appropriate (Huizinga et al., 2006; Miyake et al., 2000). Working memory is a cognitive system which temporarily maintains and manipulates information (Baddeley and Hitch, 1974; Bayliss et al., 2005). Cognitive flexibility is the ability to shift attentional focus between tasks and mental sets (Anderson, 2002; Miyake et al., 2000). Although more severe TBI often leads to worse executive dysfunction (Anderson and Catroppa, 2005; Catroppa and Anderson, 2009; Colorado Medical Society, 1991; Anderson et al., 2009a; Woodward et al., 1999), outcomes vary widely and the relationship between injury severity and degree of EF impairment cannot yet be fully explained (Anderson and Catroppa, 2005; Catroppa and Anderson, 2009). Age at injury, as a proxy for brain and cognitive development, has received increasing attention in the literature as a potential influence on post-injury outcomes; however, research on its relationship to EF after paediatric TBI is still scarce.

Paediatric TBI occurs at a time of ongoing cognitive and neural development (Anderson and Catroppa, 2005; Anderson et al., 2005, 2012, 2011). The sensitive period model states that higher cognitive functions, such as EF, are particularly vulnerable when the insult occurs at times of rapid neural maturation of the function itself and its underlying networks (Anderson et al., 2011; Crowe et al., 2012; Dennis et al., 2014). For the three main EF components discussed above, development continues well into adolescence and early adulthood (Anderson, 2002; Casey et al., 2000; De Luca et al., 2003). Although each of the three EF components has a unique developmental trajectory, early and middle childhood (preschool up to approximately 9 years) has been identified as a key period for each (Anderson, 2002; Romine and Reynolds, 2005; Best et al., 2009; Jurado and Rosselli, 2007). During this stage, prior to the full maturation of EF, children have been argued to be particularly vulnerable. In support of this sensitive period model, a recent study found that children who sustained TBI in early (before 6 years) or middle childhood (7–9 years) demonstrated lower intellectual abilities than those with TBI in late childhood (10–12 years) (Crowe et al., 2012). Other studies have also reported age-dependent cognitive outcomes, including EF, in groups of children following paediatric brain injury (e.g. TBI, congenital injuries, stroke), highlighting increased vulnerability if children were injured at an age when EF were emerging (Anderson et al., 2009a, 2010).

Despite protracted EF development throughout childhood and into adulthood (Anderson, 2002; Casey et al., 2000; De Luca et al., 2003), the impact of age at injury has rarely been investigated in patients

beyond late childhood. Results of these studies seem to indicate that impact of TBI diminishes after early and middle childhood (Anderson, 2002; Crowe et al., 2012; Romine and Reynolds, 2005; Best et al., 2009; Jurado and Rosselli, 2007). However, the sensitive period model would predict that EF are at heightened risk for disruption during adolescence as well, since brain regions involved in these skills are undergoing rapid maturation (Giedd et al., 1999; Gogtay et al., 2004). In typically developing (TD) children, adolescence is identified as a sensitive period, characterised by rapid decrease in cerebral grey matter paralleled by increases in white matter, indicating synaptic pruning and myelination and resulting in functional maturation (Giedd et al., 1999; Gogtay et al., 2004). Immaturities in adolescent EF and underlying brain substrates are clearly apparent in, for example, enhanced risk-taking behaviour as a consequence of limited inhibitory control (Blakemore and Choudhury, 2006; Blakemore and Robbins, 2012; Sawyer et al., 2012). In the TBI literature, a recent study employed a global EF index, combining performance test scores and parent-ratings of EF, found that children with severe injuries during adolescence (13–15 years) had greater impairment than children injured during late childhood (10–12 years), and similar impairments to those injured in early or middle childhood (Krasny-Pacini et al., 2017). Adolescents showed almost no recovery over the two years post insult. Generalization of these results is difficult, however, due to small sample size and inability to determine specific EF profiles (Krasny-Pacini et al., 2017). Further investigation in larger studies is warranted, to better characterise the nature of EF impairment and its association with age at injury and injury severity.

Recent evidence suggests that EF components are supported by anatomically distributed brain networks (i.e. in frontal, temporal, parietal and subcortical regions) (Lewis et al., 2004; Monchi et al., 2006; Nowrangi et al., 2014; Power et al., 2007). A promising technique to establish a link between TBI related brain lesions and EF outcomes is susceptibility-weighted imaging (SWI). SWI makes use of a three-dimensional T2\*-weighted gradient recalled echo sequence that is highly susceptible to the magnetic properties of extracellular and extravascular blood (Haacke et al., 2004; Tong et al., 2003). This technique is more sensitive than conventional imaging techniques in detecting focal as well as diffuse haemorrhagic pathology (Spitz et al., 2013; Beauchamp et al., 2011). Moreover, SWI is superior to other neuroimaging techniques such as computed tomography or conventional magnetic resonance imaging sequences in detecting micro-haemorrhages because it has increased sensitivity for revealing small traumatic axonal injuries, which may be more typical of mild TBI (Tong et al., 2003; Babikian et al., 2005; Beauchamp et al., 2011). Detecting the presence of SWI lesions can be done by visual examination, for example by radiologists, making it a useful clinical tool for diagnosis. The number and volume of lesions across the brain detected with ((sub) acute SWI analyses have been found to be predictive of general intellectual abilities from 6 months to 3 years post-injury as well as for a general neuropsychological functioning index including verbal and nonverbal memory, information processing, attention and language skills) 1–3 years post-injury (Babikian et al., 2005). The relationship between lesions detected with SWI and EF after paediatric TBI remains to be determined.

The present study extends previous research in two important ways. Firstly, given previous research has focused predominantly on severe TBI, we studied the impact of TBI across the entire spectrum of injury severity (i.e. mild, moderate, severe TBI), occurring from early childhood to adolescence. We hypothesized that, children sustaining TBI in key sensitive developmental periods including early and middle childhood and adolescence, would also demonstrate poorer EF at 6 months

and 2 years post-injury. Secondly, we investigated the relations between EF outcomes after TBI and neuropathology as detected with SWI. To that end, we examined lesions in terms of extent (i.e. how many individual regions of the brain were affected, and thus how diffuse the lesions were), number and volume. We hypothesized that a greater extent, number and volume of SWI lesions would be associated with worse EF outcomes, and that the association would be stronger for children who were injured during early and middle childhood and adolescence (i.e. when the damage to the networks underlying EF occurred during a sensitive period of EF development) than for children injured during late childhood.

## 2. Methods

### 2.1. Participants

This study represents a substudy of a prospective, longitudinal cohort study of children's cognitive and social functioning after TBI (Anderson et al., 2017; Ryan et al., 2015a). Children and adolescents with TBI were recruited at time of injury on presentation to the Emergency Department of a tertiary paediatric hospital, the Royal Children's Hospital (RCH), Melbourne, Australia. Participants represented consecutive admissions to the RCH. Children and adolescents in the TD group were recruited via local schools.

Inclusion criteria for the TBI group were: 1) aged between 5.0 and 15.0 years at time of injury; 2) documented evidence of closed head injury; 3) sufficient information (i.e. Glasgow Coma Scale, neurological and radiological findings) in medical records to determine severity of injury; 4) no documented history of neurological or developmental disorders, non-accidental injury, or previous TBI; and 5) English speaking. The TD group was required to meet inclusion criteria 1, 4 and 5 and was matched on age and sex to the group of children with TBI (Anderson et al., 2017; Ryan et al., 2015a).

For the present study, all children (i.e. those with TBI as well as TD children) were categorized into four age groups, i.e. early childhood (5–6 years), middle childhood (7–9 years), late childhood (10–12 years) and adolescence (13–15 years). The categorization is based on timing of cerebral maturational spurts as described in the literature (Giedd et al., 1999; Gogtay et al., 2004; Giza and Prins, 2006; Kolb et al., 2004; Van Praag et al., 2000) and has previously been used in investigations of cognitive outcomes, including EF, following paediatric TBI (Crowe et al., 2012; Krasny-Pacini et al., 2017; Anderson et al., 2009b).

### 2.2. Materials

#### 2.2.1. Demographics and injury variables

Demographic information was retrieved from a parent questionnaire. The Australian Socioeconomic Index 2006 was used to assign a score of 0 (e.g. labourer) to 100 (e.g. medical practitioner) to parents' occupation (McMillan et al., 2009), of which the highest score served as a measure for socio-economic status (SES). Parents were interviewed at both assessments (see 2.3) regarding the amount and type of treatment their child had received up to that point. Injury data (i.e. cause of injury, severity of injury, neurological signs, loss of consciousness, and length of hospital stay) were extracted from medical records.

#### 2.2.2. EF outcomes

Three performance-based tests and one parent-rated measure of EF were selected to assess the three main EF constructs 6 months and 2 years post-injury.

**2.2.2.1. Inhibitory control.** Walk/Don't Walk Test of Everyday Attention for Children (TEA-Ch) (Manly et al., 1994). Children are instructed to mark a box on a sheet of paper after a target tone (i.e. 'walk' sound) is presented, but not when a non-target tone (i.e. 'don't walk' sound) is presented. The tones are presented in a rhythmic fashion with the 'don't

walk' sound occurring unpredictably within the sequence. Scaled score ( $M = 10$ ,  $SD = 3$ ) calculated with the official manual (Manly et al., 1994) was used as the outcome parameter.

**2.2.2.2. Working memory.** The Digit Span (Wechsler Intelligence Scale for Children) (Wechsler, 2003). Only the digits backward trials were used, where the participant is required to repeat a sequence of digits (ranging from 0 to 9) in the reverse order as the examiner. The length of the sequence gradually increases in difficulty. The scaled score ( $M = 10$ ,  $SD = 3$ ) functioned as the outcome parameter.

**2.2.2.3. Cognitive flexibility.** Creature Counting task (TEA-Ch). Children are asked to count a number of stimuli (i.e. 'creatures'). During the task, they have to switch between counting forward and backward, as indicated by arrows pointing up or down. Before the test, the ability to count up to and down from 12 is assessed. Scaled scores ( $M = 10$ ,  $SD = 3$ ) for the total number of correct trials and the timing score (i.e. the total time taken to complete all correct trials divided by the total number of switches made during the correct trials) were computed and functioned as cognitive flexibility outcomes. Unlike the other measures, the timing score of the Creature Counting task depends to a large extent on processing speed. To control for potential influences of group differences (i.e. TBI vs TD) in processing speed on the timing measure, we assessed processing speed as a potential covariate (see 2.2.2.4).

**2.2.2.4. Processing speed.** The Processing Speed Index ( $M = 10$ ,  $SD = 3$ ) from the Wechsler Intelligence Scale for Children-IV (WISC-IV) (Wechsler, 2003), was administered to assess speed of information processing and included as a possible covariate.

**2.2.2.5. Parent-report on everyday EF.** The Behaviour Rating Inventory of Executive Function (BRIEF:parent) (Gioia et al., 2000) was used as a measure of everyday EF. T-scores on subscales corresponding to the EF as measured with the performance tests ('Inhibitory Control', 'Working Memory' and 'Shift/Flexibility') and Global Executive Composite' (GEC) were analysed. Higher scores represent more problems with everyday EF.

#### 2.2.3. Susceptibility weighted imaging (SWI)

The three main SWI outcome parameters used in the present study were the extent (total number of independent brain regions affected), total number of lesions and total lesion volume.

**2.2.3.1. Imaging acquisition.** MR images were acquired on a 3 T Siemens Trio Scanner (Siemens Medical Systems, Erlangen, Germany) fitted with a 32-Channel matrix head coil. Conventional MR sequences were performed using a standardized imaging protocol that included a SWI sequence (Beauchamp et al., 2011). SWI is a variant of the standard 3D FLASH sequence that exploits the signal loss from shortened T2\* characteristics of calcium- and deoxyhemoglobin-containing lesions. The images are T2\* weighted because of the range of acceptable TEs used in the acquisition (18–22 ms). The increased sensitivity to shortened T2\* lesions is owed to the employed image reconstruction methods. Both magnitude and phase images are reconstructed from the data set. The phase images display a high sensitivity to local susceptibility variations and are used as an image mask to be combined with the magnitude data set. The combined data set is then reconstructed using a sliding window (eight individual slices compressed into one image), minimum intensity projection data set. The total acquisition time for the MRI protocol was 31 min 53 s.

**2.2.3.2. SWI analysis.** SWI images were visually reviewed to determine the quality of the scan. Scans were coded for neuroanatomical location of lesions by a paediatric neuroradiologist and a neuropsychologist blind to patients' clinical details. Lesions were identified through visual

inspection and coded according to location (frontal, extrafrontal, subcortical) based on a modified Coffey system (Beauchamp et al., 2011; Coffey and Figiel, 1991). More specifically, signal changes in grey and white matter were coded in the following cortical and subcortical regions: frontal/temporal/parietal/occipital lobes, cerebellum, hippocampus, amygdala, corpus callosum (CC), thalamus, and basal ganglia. Scans rated positive for lesions on SWI were further investigated by manual segmentation using ITK snap (Yushkevich et al., 2006). Lesion counts were conducted using a connected component analysis of lesion masks, accounting for the possibility of the presence of multiple lesions in any independent region of the brain. Repeatability of segmentation was checked by re-segmenting 5 scans after a delay of greater than 6 months and comparing volumes using intra-class correlation (ICC). Lesion extent was calculated as the total number of brain regions showing signal abnormality (Kraus et al., 2007), thereby providing a measure of extent of TBI related structural abnormalities. Given that this measure takes into account the number of affected areas across the brain independent of the location of these lesions, it is thought to be sensitive to diffuse neuropathology (Kraus et al., 2007) and has previously successfully been used as such (Ryan et al., 2015a, 2015b).

### 2.3. Procedure

The study was approved by the RCH Human Research Ethics Committee. All participants were ascertained between 2007 and 2010. Informed consent was obtained from all parents regarding their child's participation in the study. From children older than 8 years, verbal assent was provided.

Data reported were collected at two time points: for the TBI group at 6 months and 2 years post-injury, for the TD group on recruitment and 18 months later. EF tasks were administered by trained researcher assistants. Parents completed a questionnaire regarding demographic variables and on their child's everyday EF behaviour. SWI data were collected for children with TBI between 2 and 8 weeks post-injury ( $M = 39.25$ ,  $SD = 27.64$  days). See Fig. 1 for a flow-chart of the procedure.

### 2.4. Statistical analyses

Analyses were conducted with IBM SPSS Statistics 24. For all analyses;  $\alpha$  was initially set at 0.05 and corrected for multiple testing when applicable (i.e.  $\alpha$  divided by the number of comparisons made). All data were checked for assumptions. Since non-normal distributions were

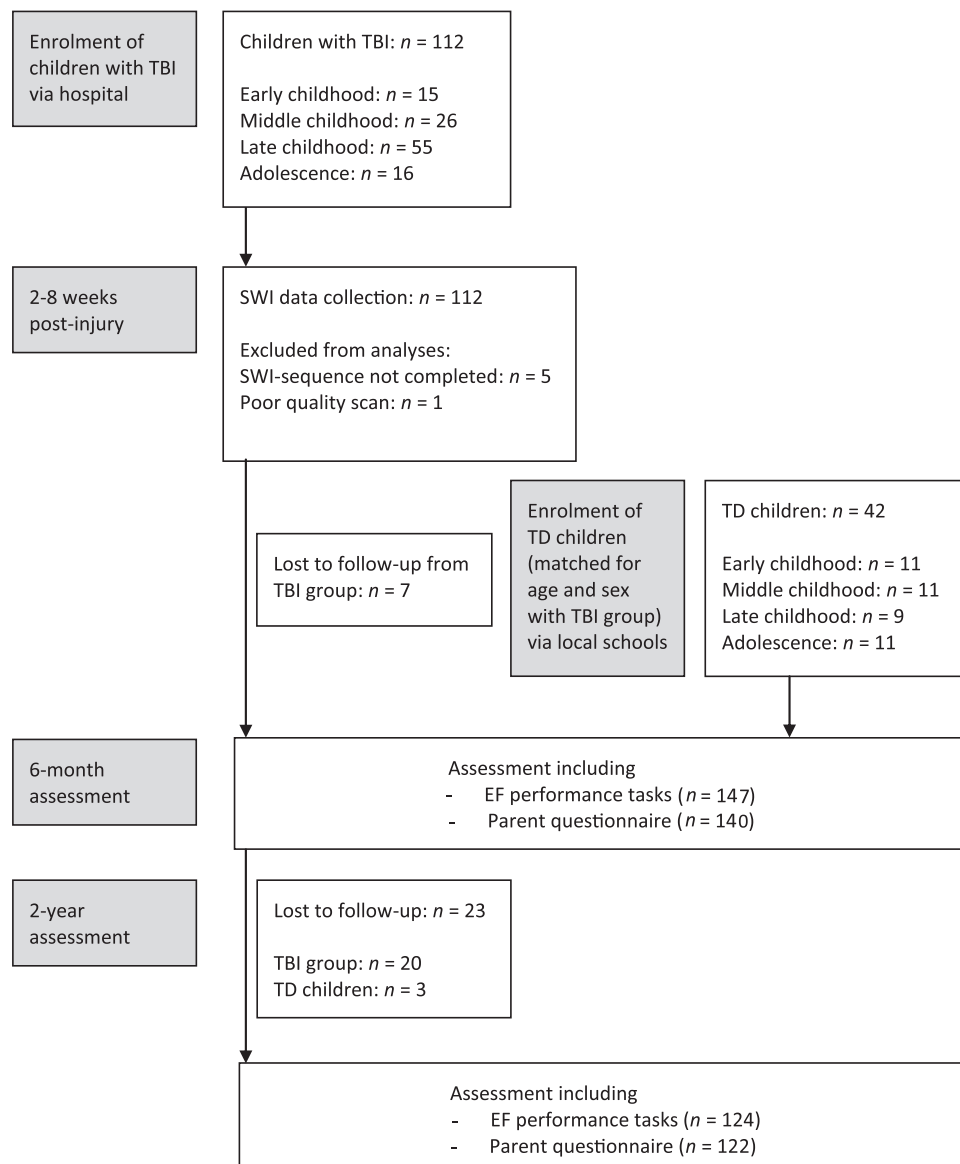


Fig. 1. Participant flow and procedure for enrolment and assessment.



found for some dependent variables, these data were transformed before analysis (see [Supplemental data 1 and 2](#)). The few identified outliers (i.e. 3 in total, distributed over the 9 dependent variables and 2 time points) were trimmed to 3 SD from the mean. Comparability of the age groups regarding demographic and injury-related variables (i.e. sex, SES, processing speed, severity of injury, neurological signs, loss of consciousness, length of hospital stay and post-TBI care) was assessed using one-way analyses of variance (ANOVA),  $\chi^2$  tests for independence or Kruskal-Wallis nonparametric tests. Similarly, children with TBI and TD were compared per age group on all but the injury-related variables mentioned above.

The influence of age group and TBI (i.e. TBI or TD) on EF performance 6 months and 2 years post-injury was examined using one-way ANOVA for the 6 months-outcome and ANCOVA for the 2-year outcome, adjusting for the 6-months outcome (Vickers and Altman, 2001). In the analyses pertaining to the timing score of the Creature Counting task, processing speed (i.e. score on PSI) was entered as covariate. To examine effect sizes, partial  $\eta$  squared ( $\eta_p^2$ ) was computed and evaluated according to Cohen's guidelines (i.e. .01 = small, .059 = medium, .138 = large) (Cohen, 1988). Due to violation of the assumption of homogeneity of variances, the influence of age and TBI on the number of correct responses on the TEA-Ch Creature Counting test as well as on the BRIEF GEC at 6 months was examined using negative binomial regression.

Given the non-parametric distributions of the SWI parameters, Kruskal-Wallis tests were used to assess whether the extent, number or volume of SWI lesions differed between the age groups in children with TBI. Kendall's Tau-b rank-order correlations were used to investigate associations between neuropathology detected with SWI (quantified by three separate indices, i.e. extent, number and volume of lesions) and EF outcomes per age group. Negative correlations were expected between SWI parameters and performance tasks (indicating that more neuropathology is related to worse EF performance), while positive correlations were expected between SWI outcomes and the BRIEF (indicating that more neuropathology is related to more EF problems in daily life). The size of the associations was evaluated according to Cohen's guidelines: .10 = small, .30 = medium, .50 = large (Cohen et al., 2013).

### 3. Results

#### 3.1. Sample characteristics

A total of 154 children, 112 with TBI and 42 TD controls, participated in this study. Given that our analyses pertained to children who had at least participated in the 6-month assessment, we excluded the 7 children who dropped out before the 6-month assessment from all further description. [Fig. 1](#) shows the flow of participants throughout the study.

Demographics and injury-related details are displayed in [Table 1](#). There were no sex differences between groups. Given differences between children with TBI and TD children in terms of SES, main analyses included SES as a covariate. For children with TBI, age groups did not differ regarding number of neurological signs, duration of loss of consciousness, length of hospital stay, and number of post-TBI interventions (e.g. speech pathologist, psychologist, occupational therapist) up to the 6-month as well as the 2-year assessment. The proportion of children who had required surgical intervention was the same across all age groups.

Participants with TBI were categorized as 1) mild TBI ( $n = 52$ ): Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) between 13 and 15, no signs of mass lesion on clinical MRI or CT (SWI not taken into account for classification); 2) complicated mild TBI ( $n = 14$ ): GCS 13–15, signs of mass lesion on clinical MRI or CT; 3) moderate TBI ( $n = 25$ ): GCS between 9 and 12, and/or signs of mass lesion or other evidence of specific injury on clinical MRI or CT, and/or neurological impairment; 4) severe TBI ( $n = 14$ ): GCS 3–8, and/or evidence of mass lesion or other specific injury on clinical MRI or CT, and/or neurological impairment. Age groups of children with TBI did not differ in terms of injury severity,  $\chi^2(3) = 4.802, p = .187$ . Given significant differences between children with TBI and TD children in terms of PSI score 6 months ( $F(1144) = 6.390, p = .013, \eta_p^2 = .043$ ) and 2 years ( $F(1, 121) = 16.664, p < .001, \eta_p^2 = .122$ ) post-injury, this score was added as a covariate in the analyses of the Creature Counting timing score, which partially depends on processing speed.

Between the 6-month and 2-year assessment, 23 participants (3 TD) dropped out from the study, leaving a sample of  $n = 124$  to analyse for the 2-year assessment. Participants and drop-outs were comparable on all variables depicted in [Table 1](#), except for age of the TD children: the

**Table 1**  
Characteristics of TBI and TD age groups.

	Early childhood		Middle childhood		Late childhood		Adolescence		Statistics
	TBI	TD	TBI	TD	TBI	TD	TBI	TD	
<b>Demographics</b>									
n	14	11	24	11	52	9	15	11	
Sex [male], n (%)	7 (50)	7 (63)	16 (67)	4 (36)	36 (69)	7 (78)	13 (87)	5 (45)	NS
SES M (SD) <sup>1</sup>	74.38 (18.16)	80.43 (6.12)	63.44 (23.86)	75.77 (18.66)	63.16 (23.96)	70.72 (18.16)	76.90 (18.46)	79.53 (10.15)	TBI vs TD: $F(1, 144) = 5.048, p = .026, \eta_p^2 = .034$
Age at injury, M (SD)	6.28 (0.33)	–	8.23 (0.86)	–	11.36 (0.85)	–	13.92 (0.44)	–	–
Age at 6-month assessment, M (SD)	6.82 (0.36)	6.70 (0.49)	8.77 (0.84)	8.60 (0.82)	11.86 (0.84)	11.56 (1.07)	14.46 (0.46)	14.27 (0.73)	–
Age at 2-year assessment, M (SD)	8.24 (0.44)	8.27 (0.58)	10.24 (0.86)	10.14 (0.84)	13.27 (0.78)	12.96 (1.03)	15.74 (0.70)	15.67 (0.69)	–
<b>Injury characteristics</b>									
Lowest GCS in 24 h, M (SD)	10.71 (4.32)	–	13.17 (2.81)	–	13.06 (2.91)	–	11.57 (4.13)	–	NS
Neurological signs, M (SD)	1.07 (0.27)	–	1.42 (0.78)	–	1.44 (0.67)	–	1.20 (0.41)	–	NS
<b>Injury cause</b>									
Falls, n (%)	10 (71)	–	15 (63)	–	28 (54)	–	10 (67)	–	NS
MVA, n (%)	3 (21)	–	4 (17)	–	14 (27)	–	3 (20)	–	NS
Others, n (%)	1 (7)	–	5 (21)	–	10 (19)	–	2 (13)	–	NS

GCS = Glasgow Coma Score, MVA = Motor vehicle accident, SES = Socio-economic status, M = mean, SD = standard deviation, TBI = children with traumatic brain injury, TD = typically developing children. <sup>1</sup> Significant difference between TBI and TD.

three drop-outs were significantly older than the children who still participated. However, without these three TD children, the age of TD children and children with TBI remained comparable in all age groups. There was some missing data for parent questionnaire: the number of questionnaires included in the analysis was  $n = 140$  at 6 months, and  $n = 122$  at 2 years.

### 3.2. EF outcomes

#### 3.2.1. EF performance tests

Mean scores per age group on the performance-based EF tests are displayed in Table 2. Inhibitory control at the 2-year assessment was influenced by an age by TBI interaction,  $F(3, 112) = 3.269$ ,  $p = .024$ ,  $\eta_p^2 = .080$ . Simple effects analyses corrected for multiple testing revealed no significant differences between children with TBI and TD children. Visual inspection of the results and examination of the effect sizes suggested that the result in the main analysis was driven by differences between children with TBI and TD children in the early childhood group,  $F(1, 18) = 4.773$ ,  $p = .042$ ,  $\eta_p^2 = .210$ , and in the adolescence group,  $F(1, 19) = 4.231$ ,  $p = .054$ ,  $\eta_p^2 = .182$ , with children with TBI performing worse than TD children. No other interactions between age and TBI or main effects of TBI were found. For more details on the results of the analyses, see Supplemental data 1.

#### 3.2.2. Parent-report on everyday EF

Mean scores on the BRIEF subscales per age group can be found in Table 3. For the Inhibitory Control scale at the 2-year assessment, there was main effect of TBI,  $F(1, 108) = 4.778$ ,  $p = .031$ ,  $\eta_p^2 = .042$ , with scores indicating that children with TBI have more inhibitory problems than TD children. No further effects of age by TBI or TBI alone were found. For more details, see Supplemental data 2.

#### 3.3. Neuroanatomical location of lesions detected using SWI

Of the participants with TBI, five did not complete the SWI sequence. One scan was rejected due to poor quality and this participant's data were excluded from further analyses incorporating SWI findings. Thus, data from 106 participants with TBI are reported. Lesions were detected in 37 patients (35%) across all severity groups. Lesions were most prominent in frontal regions (frontal only = 15 patients, frontal + extrafrontal = 6, frontal + other regions [CC = 1, deep grey + CC = 1, cerebellum = 1, cerebellum + CC = 1]), followed by extrafrontal regions only ( $n = 6$ ). A small number of patients ( $n = 4$ ) had lesions in several areas (frontal + extrafrontal + cerebellum = 2, frontal + extrafrontal + deep grey = 1, frontal + extrafrontal + CC = 1). Very few patients had lesions solely in the CC ( $n = 1$ ), cerebellum ( $n = 1$ ) regions. The number of lesions varied from 1 to 70. Segmentation procedures were reliable, with an intra-rater ICC score of 0.987 (95% confidence interval = 0.911–0.999).

**Table 2**

Scores on performance-based EF test per age group, M (SD).

		Early childhood		Middle childhood		Late childhood		Adolescence	
		TBI	TD	TBI	TD	TBI	TD	TBI	TD
Inhibitory control (Walk/Don't Walk)	6 months	6.15 (3.24)	6.55 (2.54)	7.29 (3.17)	8.45 (4.32)	8.24 (3.74)	8.00 (4.56)	6.67 (3.48)	6.82 (2.99)
	2 years <sup>1</sup>	<b>7.00 (3.52)</b>	<b>10.73 (4.56)</b>	<b>8.33 (4.06)</b>	<b>8.64 (3.80)</b>	<b>8.32 (3.20)</b>	<b>6.88 (3.09)</b>	<b>8.57 (3.61)</b>	<b>11.33 (3.91)</b>
Working memory (Digit Span Backward)	6 months	10.62 (2.69)	10.64 (2.83)	9.67 (2.46)	10.00 (2.65)	9.10 (2.69)	9.44 (3.50)	8.07 (2.60)	10.55 (2.07)
	2 years	9.27 (2.49)	9.73 (2.76)	10.50 (3.26)	10.18 (2.56)	9.27 (3.15)	8.63 (3.85)	8.57 (2.47)	11.22 (3.35)
Cognitive flexibility (Creature Counting Correct)	6 months	8.23 (3.09)	10.09 (4.28)	10.08 (3.17)	9.00 (3.58)	9.57 (3.47)	12.44 (1.42)	12.60 (2.13)	12.18 (2.32)
	2 years	9.72 (2.37)	11.45 (3.14)	10.83 (2.20)	10.81 (2.93)	10.93 (2.32)	10.13 (2.70)	11.07 (2.53)	12.44 (1.67)
Cognitive flexibility (Creature Counting Timing Score)	6 months	8.17 (2.64)	10.57 (2.44)	8.87 (3.82)	11.00 (3.64)	8.89 (3.09)	10.56 (2.24)	9.33 (3.85)	11.09 (1.70)
	2 years	9.91 (3.05)	11.00 (2.36)	11.17 (3.28)	11.82 (2.99)	10.64 (3.04)	11.13 (2.30)	10.57 (2.82)	11.44 (1.01)

EF = executive function, M = mean, SD = standard deviation, TBI = children with traumatic brain injury, TD = typically developing children.

Note. The values displayed pertain to the standard scores of the untransformed variables.

<sup>1</sup>  $p = .024$  for the interaction between TBI/TD and age group at the 2-year assessment.

The proportion of children with SWI lesions was similar across age groups,  $\chi^2(6) = 4.413$ ,  $p = .657$ . There were no differences between age groups in terms of extent of the lesions (i.e. number of individual brain regions affected),  $\chi^2(3) = 0.438$ ,  $p = .932$ , number of lesions,  $\chi^2(3) = 0.541$ ,  $p = .910$ , or volume of the lesions,  $\chi^2(3) = 1.000$ ,  $p = .801$ .

#### 3.3.1. Associations between EF outcomes and neuropathology

Correlation coefficients are reported in Supplemental data 3. For small samples (such as in our individual age groups) it is especially important to not only pay attention to the size of the correlations but also to the test of significance, to decrease the chance of spurious findings. None of the correlation analyses were significant after correction for multiple testing. Results significant at an  $\alpha$ -level of .05 will be discussed in more detail, but should be interpreted with caution. In the middle childhood group, number of lesions was significantly positively associated with the score on the Digit Span Backward test at the 6-month assessment, suggesting that children who were injured during middle childhood had a higher working memory score if they had more lesions. In the adolescence group, medium to large correlations were found between all SWI variables (i.e. extent, number and volume of lesions) and the Working Memory, Shift/flexibility, and General Executive Component scores of the BRIEF at 6-month post-injury, indicating more everyday EF problems in these domains and/or overall with more neuropathology. These associations were not found 2 years post-injury.

### 4. Discussion

In this study, we tested the sensitive period model for EF outcomes in a sample consisting of children and adolescents with TBI, and we explored the value of SWI in relation to EF outcomes. Consistent with the sensitive period model (Anderson et al., 2011; Crowe et al., 2012; Dennis et al., 2014) and results from previous studies (Anderson et al., 2009a, 2010; Crowe et al., 2012; Krasny-Pacini et al., 2017), we hypothesized that children who sustained TBI during early or middle childhood or adolescence (i.e. sensitive periods for EF development) would show worse EF performance compared to controls than children who were injured during late childhood.

First, results indicate that, of the three EF assessed, inhibitory control was most sensitive to the impact of the injury. For inhibitory control performance, differences between children with TBI and TD children seemed to depend on age at injury (to be discussed below), while the standardized parent report measures indicated that 'everyday' inhibitory control was significantly poorer than TD controls regardless of age at injury. Both for the performance measure and for the parent report measure, the difference between children with TBI and TD children only emerged at the 2-year assessment. These results suggest that clinicians should closely monitor the potential risk of inhibitory

**Table 3**  
BRIEF scores per age group, M (SD).

		Early childhood		Middle childhood		Late childhood		Adolescence	
		TBI	TD	TBI	TD	TBI	TD	TBI	TD
Inhibitory Control	6-month assessment	47.43 (10.27)	49.64 (7.07)	47.95 (9.16)	44.82 (5.29)	51.72 (12.45)	48.56 (5.48)	50.00 (15.12)	46.18 (4.81)
	2-year assessment <sup>1</sup>	<b>49.18 (11.75)</b>	<b>46.27 (4.63)</b>	<b>48.78 (9.60)</b>	<b>42.64 (3.72)</b>	<b>51.80 (13.71)</b>	<b>49.00 (5.53)</b>	<b>51.23 (15.28)</b>	<b>45.33 (6.34)</b>
Working Memory	6-month assessment	50.93 (9.86)	44.46 (11.77)	47.14 (6.34)	44.55 (5.91)	53.84 (11.15)	47.00 (8.90)	48.73 (12.46)	54.00 (10.87)
	2-year assessment	51.36 (11.63)	44.64 (7.06)	47.44 (8.49)	43.73 (5.18)	52.97 (12.65)	49.63 (8.90)	52.15 (14.08)	49.44 (8.59)
Shift/Flexibility	6-month assessment	49.64 (10.51)	45.18 (6.23)	47.19 (8.23)	43.73 (8.82)	47.91 (12.19)	46.67 (7.00)	48.27 (12.29)	47.27 (7.96)
	2-year assessment	51.73 (12.28)	44.64 (10.09)	44.56 (7.17)	44.81 (6.65)	47.46 (9.70)	46.13 (6.31)	51.46 (13.57)	44.67 (5.00)
GEC	6-month assessment	48.23 (9.29)	46.00 (3.64)	45.10 (6.35)	43.91 (4.09)	51.53 (11.42)	46.89 (7.56)	48.20 (11.74)	50.00 (5.87)
	2-year assessment	49.27 (10.85)	43.09 (3.72)	44.17 (7.70)	43.82 (4.92)	51.05 (12.34)	48.00 (9.01)	49.77 (11.94)	46.11 (6.05)

BRIEF = Behaviour Rating Inventory of Executive Function, GEC = Global Executive Composite, M = mean, SD = standard deviation, M = mean, SD = standard deviation, TBI = children with traumatic brain injury, TD = typically developing children.

Note. The values displayed pertain to the standard scores of the untransformed variables.

<sup>1</sup>  $p = .031$  for difference between TBI and TD across age groups at the 2-year assessment.

control impairments in children across the spectrum of TBI severity, even among children with milder generalised injuries. On the other hand, working memory and cognitive flexibility, when assessed as separate EF components, were not impaired at the group level. Different EF seem to be differentially affected by TBI, which is in line with previous findings of (long-term) EF outcomes after paediatric TBI (Beauchamp et al., 2011).

While the main analyses of inhibitory control performance revealed an interactive effect of TBI and age at injury on this specific EF outcome, simple effects analyses showed no significant differences within the four individual age groups. Discussion of the following results is therefore based on the large effect sizes that we found for differences between children with TBI and TD children in the early childhood group and the adolescence group, but not in the middle childhood group and late childhood groups. The results should be interpreted with caution and we further reflect on this when discussing the limitations of the present study below.

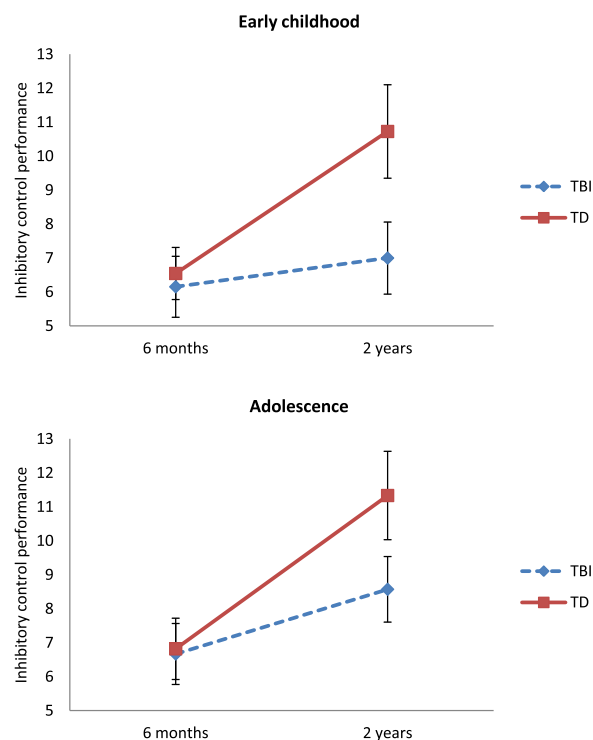
Partly in line with our hypotheses, the interaction between age at injury and TBI on 2-year inhibitory control outcome seemed to emerge due to differences between children with TBI and TD children in the early childhood and adolescence groups, but not for children injured during middle and late childhood. More specifically, compared to TD controls, the early childhood and the adolescence TBI groups seemed to have poorer inhibitory control but only at the 2-year assessment. When inspecting the scores within the age groups (see Fig. 2), TD children in both the early childhood group and the adolescence group seemed to make progress from the 6-month to the 2-year assessment. For children with TBI, this ‘maturation’ effect was not as apparent or pronounced. This finding is in line with the sensitive period model stating that impact during a period of rapid neural network development has detrimental consequences for the maturation of the cognitive functions underlying these developing networks (Anderson et al., 2011, 2010; Dennis et al., 2014). The emergence of this effect only at the 2-year assessment corresponds with the notion that after paediatric brain injury, deficits in higher-order skills may emerge later in development when these skills are expected to be at a stage of becoming established and consolidated (Giza and Prins, 2006; Middleton, 2001). Inhibitory control has been known to develop and mature in early childhood (Romine and Reynolds, 2005; Jurado and Rosselli, 2007) explaining the vulnerability of children injured during this developmental period to the impact of TBI. Our finding that next to early childhood, adolescence seems to be a vulnerable period for impact on inhibitory control supports further the notion that EF continue to develop throughout adolescence and even adulthood (Anderson, 2002; Casey et al., 2000; De Luca et al., 2003).

Summing up: i) maturation and establishment of inhibitory control may be particularly vulnerable to the effects of TBI; ii) there is a need for long-term (minimum 2 years) follow-up following TBI as EF

difficulties (particular in terms of inhibitory control) may not be evident acutely; iii) both early childhood and adolescence could be periods during which EF are sensitive to disruption due to injury. Studies into the effect of TBI should therefore consider investigating these children as vulnerable groups, separately from children who are injured during e.g. middle or late childhood. However, larger group studies are warranted to confirm the vulnerability of these particular age groups.

#### 4.1. Associations of EF outcomes with neuropathology

Our findings showed that children with more (i.e. higher number) and more diffuse (i.e. greater extent) TBI-related neuropathology had worse EF outcomes compared to children with less (distributed) neuropathology, when injured during adolescence. This is in line with previous studies reporting associations between greater lesion burden and poorer cognitive functioning, such as intellectual ability (Babikian et al., 2005; Beauchamp et al., 2013) and social cognitive abilities



**Fig. 2.** Inhibitory control performance for the early childhood and adolescence groups over time, separate for children with traumatic brain injury (TBI) and typically developing (TD) children.



(Ryan et al., 2015a). However, EF outcomes between children with TBI and TD children sometimes differed, independent of SWI indices. Previous studies have shown that SWI markers (i.e. number, volume and/or extent of lesions) combined with data on age at injury and injury severity (i.e. GCS) only explain 6.5–29.7% of outcome variance in measures of intellectual ability and cognitive functioning (including EF) (Babikian et al., 2005; Beauchamp et al., 2013). Combined with the results of our study, these findings suggest that other non-injury related factors (e.g., pre-injury child factors, environment (Anderson et al., 2012; Anderson et al., 2006; Chapman et al., 2010)) may be important determinants of (long-term) cognitive (e.g. EF) outcomes after TBI.

A contra-intuitive correlation emerged between a greater number of lesions and a higher working memory performance 6 months (but not 2 years) post-injury in children who sustained a TBI during middle childhood. Similarly, in a previous study, children aged 8–15 with mild complicated TBI (i.e. showing abnormalities on an MRI scan) were found to perform better on a working memory task than children with mild TBI without indications of neural pathology (Maillard-Wermelinger et al., 2009). These results suggest that for outcomes in some cognitive domains, injury related factors alone are not sufficient to explain variability in outcome and recovery post-TBI. Again, this emphasizes the importance of taking into account non-injury related factors as potential contributors to EF outcomes.

#### 4.2. Study strengths and limitations

A particular strength of our study was the inclusion of adolescence as a separate age group. As our results indicate, TBI sustained during adolescence might have long-term negative impact on EF outcomes. This should be taken into account in clinical practice or future research after paediatric TBI. Second, we compared children with TBI to matched control groups of TD children. In contrast to previous studies that did not include a control group when investigating EF outcomes after TBI over time (Krasny-Pacini et al., 2017), this enabled us to control for practice effects that might occur when the same tasks or questionnaires are repeatedly completed. Finally, we included performance-based tasks as well as an ecologically valid, parent-reported measure for EF. Including both types of measurements is important, given that they are not always highly correlated (Vriezen and Pigott, 2002), and are sometimes even thought to assess different aspects of EF (Anderson et al., 2010, 2009b).

Results of the present study also have to be interpreted in the light of a number of limitations. Firstly, in order to evaluate the sensitive period model in relation to EF outcomes, we divided our sample into four age groups based on timing of cerebral maturational spurts (Giedd et al., 1999; Gogtay et al., 2004; Giza and Prins, 2006; Kolb et al., 2004; Van Praag et al., 2000). This approach has a strong theoretical basis in developmental biology, with brain and cognitive development best being conceptualized in a stage-based manner characterised by peaks and plateaus of rapid neural development and refinement in neural networks (Kolb et al., 2004). Additionally, age group categories are of clinical utility when making clinical decisions related to treatment and (long-term) follow-up. However, age is inherently a continuous variable and using age categories leads to arbitrary (though well-founded) division of the sample. Future studies may consider analysing the influence of age at injury on EF using age at injury as a continuous predictor to better take this into account.

Second, while our overall sample was large (i.e. 105 children with TBI and 42 TD children included in the analyses), age-at injury findings should be interpreted with caution due to smaller sample sizes of the various developmental age groups. For example, while the main analysis of the inhibitory control score 2 years post-injury yielded a significant interaction between age group and TBI, post hoc tests were insufficiently powered. Similarly, correlation coefficients between EF outcomes and SWI variables are based on a small number of children per group, potentially leading to missing important correlations

because they did not reach significance on the one hand, as well as increasing the possibility of chance findings on the other hand (e.g. the contra-intuitive correlation between a greater number of lesions and a higher working memory performance in middle childhood). Given the limited sample size of the present study, we were not able to perform regression analyses to investigate predictive influence on EF outcomes of a large number of predictors such as SWI markers, age at injury, injury severity, pre-injury abilities and family functioning. Future studies could consider building on our findings that SWI markers may be valuable, in addition to other factors, when aiming to identify children at risk for negative EF outcomes.

Third, previous studies investigating age-dependent effects of TBI included children from age 3 on in the early childhood group, while in the present study only children from age 5 on were included. Age range in the present study was based on available social and neurodevelopmental measures. Third, the performance tests of the TEA-Ch, used to measure inhibitory control and cognitive flexibility, were originally designed only for children and adolescents up to age 16 (Manly et al., 1994). While all participants were below that age at time of entering the study, eight adolescents (5 with TBI, 3 TD) had passed that age at the 2-year assessment, with their age ranging from 16.00 to 16.83 years. In the present study, 5 of these participants (3 with TBI, 2 TD) achieved the highest possible number of correct items on the Creature Counting test, potentially suggesting ceiling effects on this test. On the other EF tests, these participants did not reach the highest possible score. Since the highest score on the Creature Counting test was achieved roughly as often by TD adolescents as by adolescents with TBI, it is not expected that ceiling effects had a large influence on our findings. However, future studies might want to use tests that are intended for older children, particularly when investigating vulnerability of children injured during adolescence. Lastly, children participated in the SWI procedure between 2 and 8 weeks post-injury. TBI is associated with both primary and secondary injury mechanisms that may affect the developmental trajectory underlying EF outcome. Results of neuroimaging may differ depending on the timing of scanning. While age-at-injury groups did not differ in terms of mean time between injury and scanning, earlier scanning to detect micro-haemorrhagic lesion in the acute phase may potentially be more valuable in predicting EF outcome.

#### 5. Conclusions

Inhibitory control measured with a performance task as well as rated by a parent is particularly vulnerable to the long-term impact of TBI, with children with TBI scoring worse than TD children 2 years post-injury. Early childhood and adolescence seem to be developmental stages during which children are particularly vulnerable to the negative impact of brain injury, supporting a non-linear relationship between age at injury and outcome, and thus a 'sensitive period' model. However, these results need to be confirmed in future studies and larger sample. Relations between neuropathology as detected with SWI and EF outcomes (i.e. everyday EF behaviour) seem to be strongest during sensitive developmental periods, in this case of EF middle childhood and adolescence. SWI analyses are based on visual inspection of scans, not requiring extensive amounts of sophisticated analyses. SWI is a useful clinical tool for acute TBI diagnosis, and our results suggest that it might be of added value for predicting EF outcomes of adolescents who sustain a TBI. Considering both age at injury and neuropathology detected with SWI may help identify those at a higher risk for negative (long-term) EF outcomes.

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## Declarations of interest

The authors report no conflict of interests.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuropsychologia.2018.12.004.

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